Preparation of new axially chiral bridged 2,2′-bipyridines and pyridyl monooxazolines (pymox). Evaluation in copper(I)-catalyzed enantioselective cyclopropanation†

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Received 31st January 2007, Accepted 12th March 2007
First published as an Advance Article on the web 23rd March 2007
DOI: 10.1039/b701549f

This work reports the synthesis of new axially chiral bridged 2,2′-bipyridines **1** and pyridylmonooxazolines (pymox) **2**. The potential of these new axially chiral *N*,*N*-ligands was evaluated in asymmetric catalytic cyclopropanation of styrene derivatives **22a–c** with diazoesters **21a**,**b**. While 2,2′-bipyridines **1a–c** afforded the corresponding cyclopropanes **23a–f** in up to 65% ee, pymoxs **2a–e** gave somewhat lower enantioselectivities (up to 53% ee). Both classes of ligands produced *trans*-cyclopropanes **23a–f** as the major isomer, although with modest diasteroselectivities (56 : 44 to 78 : 22). A structure-stereoselectivity relationship study of ligands **1** and **2** identified the chiral biaryl axis as being mostly responsible for the enantioselective performances of these ligands.

Introduction

Of the many types of *N*,*N*-ligands that have been designed for asymmetric catalysis, chiral non-racemic 2,2′-bipyridines have emerged as an effective class of chiral inducers in a large number of catalytic processes, such as allylic oxidation, hydrosilylation, allylic substitution and cyclopropanation.[1] Only a few examples of 2,2′-bipyridines bearing an element of axial chirality have been reported so far in the literature. This may be explained by the lack of general and straightforward stereoselective methods giving access to axially chiral 2,2′-bipyridines. The main route to these axially chiral ligands generally required a final resolution step by preparative chiral HPLC.[15e] In an original approach initially reported by Botteghi,[2] the configuration of a biaryl axis was controlled by bridging two aryl units with a chiral appendage derived from tartaric acid. More recently, Hayashi has developed a similar strategy for the preparation of atropoisomeric 2,2′-bipyridine *N*,*N*′-dioxides,[3] using a chiral binaphthalene linkage to connect the two pyridine moities (Fig. 1).

Pyridyl monooxazolines (pymox) represent another important class of *N*,*N*-ligands, which have already been shown to be effective in various asymmetric catalytic processes.[4] To the best of our knowledge, the design and evaluation in asymmetric catalysis of pymox ligands bearing an element of axial chirality has not been reported so far.

We have previously reported the preparation of axially chiral bridged biaryl systems by means of Meyers' methodology.[5] The lactamization of biaryl keto-acids with phenylalaninol provided axially chiral bicyclic lactams in good yields and excellent diastereoselectivity. In this process, the axial configuration of the biaryl unit is subordinated to the newly generated *N*,*O*-acetal stereocenter of the oxazolidinone ring (Scheme 1).

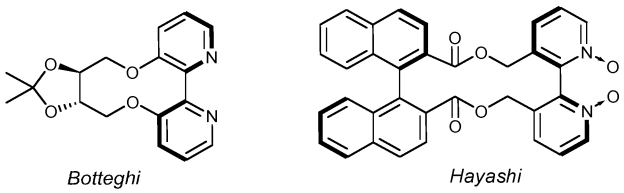
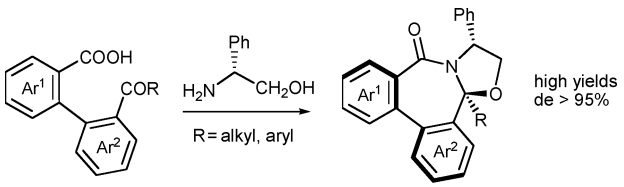


Fig. 1 Axially chiral bridged 2, 2′-bipyridines.



Scheme 1 Design of an axially chiral bridged biaryl framework by means of Meyers' methodology.

We reasoned that this atroposelective lactamization could provide a useful synthetic approach for the construction of new axially chiral ligands. In this context, we report herein the preparation of a series of axially chiral 2,2′-bipyridines **1** and pyridyl monooxazolines **2** based on the functionalization of these chiral 7,5-fused bicyclic lactams (Fig. 2). A preliminary evaluation of their potential in enantioselective cyclopropanation is also reported (Fig. 2).

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† Electronic supplementary information (ESI) available: Syntheses of ligands **1c**, **2d**,**e**; X-ray structure of 2,2′-bipyridine **1a**. See DOI: 10.1039/b701549f

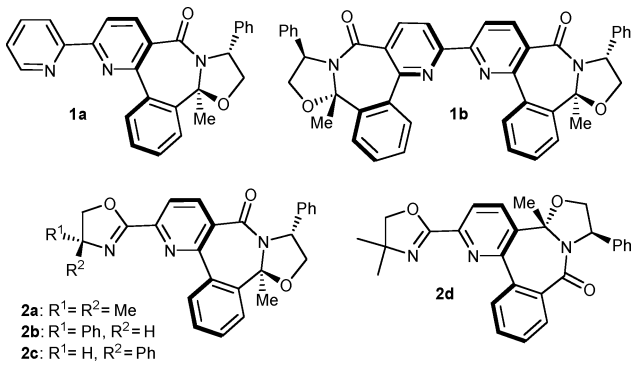
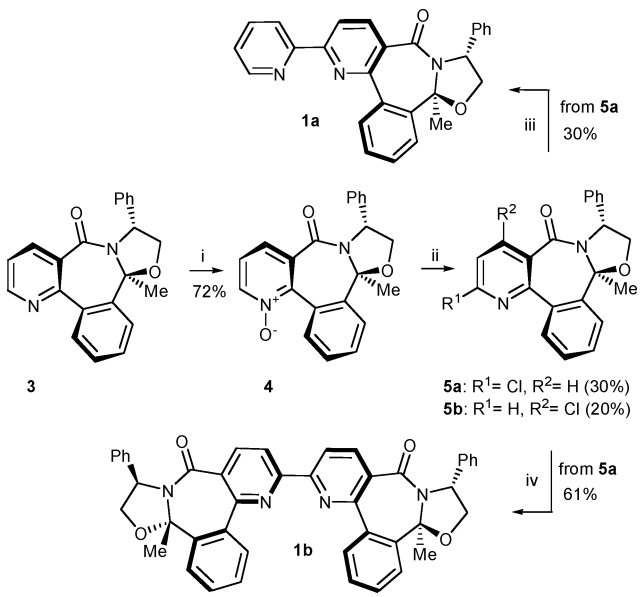


Fig. 2 Design of new axially chiral 2,2′-bipyridines **1** and pymox **2**.

Results and discussion

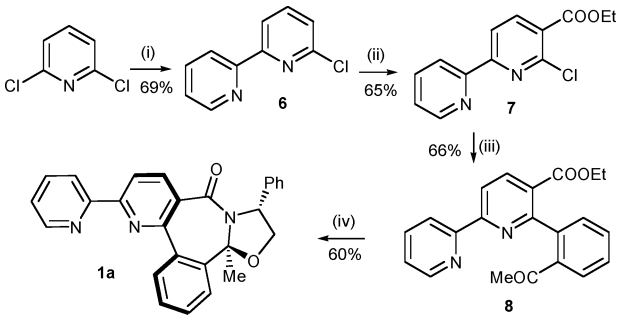
Preparation of 2,2′-bipyridyl ligands 1a,b

An initial route was investigated by functionalization of the lactam **3** previously reported in our laboratory.[5] Subsequent to *N*-oxidation of lactam **3** with *m*-CPBA, the resulting pyridine *N*-oxide **4** was treated with $POCl_3$ providing the desired chloropyridine **5a** in a modest yield (30%) along with the undesired regioisomer **5b** (20%). Initial attempts to obtain ligand **1a** by a Negishi cross-coupling reaction between **5b** and 2-pyridylzinc bromide failed, leading in most cases to the recovered starting chloropyridine **5a**. Finally, a Stille cross-coupling reaction between chloropyridine **5a** and 2-(tributylstannyl)pyridine afforded the desired C_1-symmetric 2,2′-bipyridyl **1a** in a modest yield of 30%. The C_2-symmetric 2,2′-bipyridyl ligand **1b** was obtained by a nickel-mediated homo-coupling reaction[6] of chloropyridine **5a** in 61% yield (Scheme 2).



Scheme 2 Preparation of 2,2′-bipyridines **1** by means of homo- and cross-coupling reactions from **5a**. *Reagents and conditions*: (i) CH_2Cl_2, *m*-CPBA, rt (72%); (ii) CH_2Cl_2, NEt_3, $POCl_3$, rt, 30 min, then reflux for 1 h (30% of **5a**); (iii) 2-(tributylstannyl)pyridine, toluene, $Pd(PPh_3)_4$, reflux, 24 h (30%); (iv) DMF, $NiCl_2$ $6H_2O$, Zn, PPh_3, 60 °C, 4 h (61%).

An alternative route was explored for the preparation of 2,2′-bipyridyl ligand **1a** wherein the atroposelective lactamization takes place in the last step of the reaction sequence (Scheme 3). The 2,6-dichloropyridine was first cross-coupled under Stille conditions with 2-(tributylstannyl)pyridine[7] to give the bipyridine **6** in 69% yield. This coupling step required the use of a large excess of 2,6-dichloropyridine to prevent the formation of the undesired terpyridine. Bipyridine **6** was subsequently subjected to *ortho*-lithiation in the presence of LDA at −78 °C for 1 h. The lithiated species was then trapped with ethyl cyanoformate to furnish **7** in 65% yield. A Suzuki cross-coupling reaction between this intermediate and 2-acetylphenylboronic acid furnished the lactamization precursor **8** in 66% yield. In the presence of (*R*)-phenylglycinol and under classical dehydrating conditions, the keto-acid **8** afforded ligand **1a** in 60% yield. Analysis of the ^1H NMR spectrum of the crude product revealed the presence of a single diastereoisomer (Scheme 3).



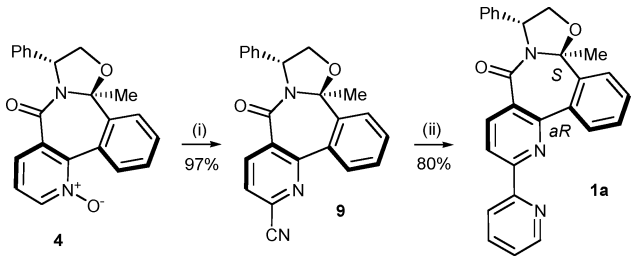
Scheme 3 Preparation of 2,2′-bipyridine **1a** by atroposelective lactamization of **8**. *Reagents and conditions*: (i) 2-(tributylstannyl)pyridine, toluene, $Pd(PPh_3)_4$, reflux, 24 h (69%); (ii) LDA, THF, −78 °C, 1 h then ethyl cyanoformate, −78 °C, 1 h (65%); (iii) 2-acetylphenylboronic acid, toluene, K_2CO_3, EtOH, H_2O, $Pd(PPh_3)_4$, reflux, 48 h (66%); (iv) (*R*)-phenylglycinol, toluene, reflux, 6 days (60%).

Finally, the last approach investigated was the cobalt-catalyzed [2 + 2 + 2] cycloaddition of cyanopyridine **9** and acetylene under photochemical conditions.[8] The pyridine *N*-oxide **4** was subjected to the Reissert reaction conditions, affording the required cyanopyridine **9** in 97% yield. The cobalt-catalyzed [2 + 2 + 2] cycloaddition was carried out in toluene under very mild conditions, at ambient temperature and pressure in the presence of CpCo(cod)[9] as the catalyst source. Ligand **1a** was isolated in 80% yield after flash chromatography. This approach provide rapid and straightforward access to ligand **1a** in good yield. An X-ray crystallographic analysis‡ of **1a** revealed an *S* configuration for the newly created *N*,*O*-acetal stereocenter and an *R* configuration for the biaryl axis that connects the phenyl and the bipyridyl unit. It was found that these two aryl moities adopt a rather flat dihedral angle of 38°(Scheme 4).[10]

Preparation of pyridylmonooxazolines (pymox) 2a–d

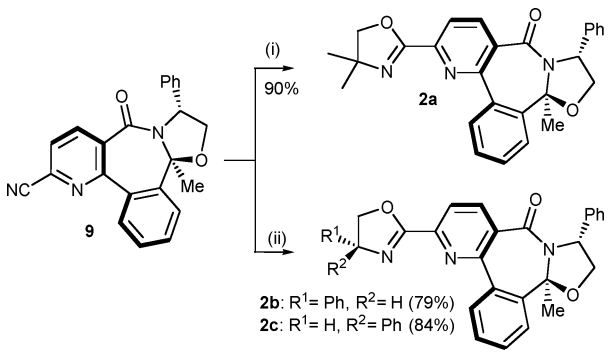
The preparation of the pymox ligands **2a–c** was accomplished from the cyanopyridine **9** intermediate by formation of Meyers' oxazoline. Pymox **2a** was straightforwardly obtained in 90% yield

‡ CCDC reference number 637822. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b701549f



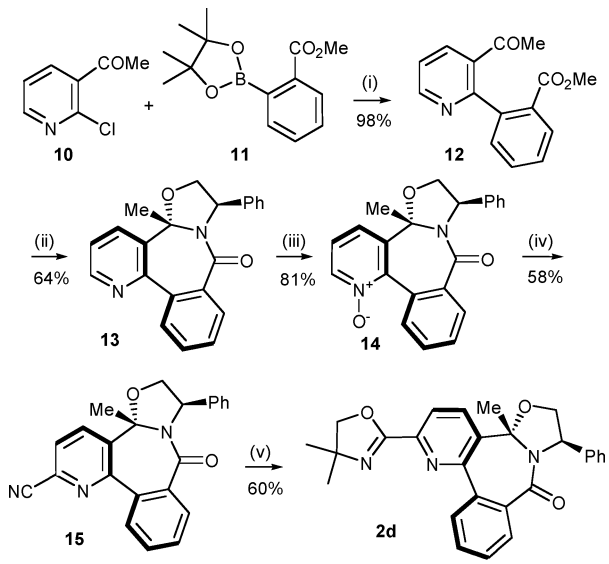
Scheme 4 Preparation of C_1-symmetric 2,2′-bipyridine **1a** *via* [2 + 2 + 2] photocycloaddition of **9** with acetylene. *Reagents and conditions*: (i) $(Me)_2NCOCl$, TMSCN, CH_2Cl_2, rt, 48 h (repeated twice) (97%); (ii) toluene, [CpCo(cod)], acetylene, rt, hν (420 nm), 5 h (80%).

by reacting 2-amino-2-methylpropanol and **9** in the presence of dry $ZnCl_2$ in refluxing chlorobenzene.[11] Attempts to apply these reaction conditions with (*R*)- or (*S*)-phenylglycinol failed, leading in both cases to the formation of tarry materials. We finally succeeded *via* the formation of an imidate intermediate, which was then transformed into the desired pymox **2b**,**c** by reaction with (*R*)- or (*S*)-phenylglycinol in refluxing chorobenzene.[12] This method could be scaled up to multigram quantities affording **2b**,**c** in 79% and 84% yields, respectively (Scheme 5).



Scheme 5 Preparation of pymox **2a–c** from cyanopyridine **9**. *Reagents and conditions*: (i) $ZnCl_2$, 2-amino-2-methylpropanol, chlorobenzene, reflux, 48 h (90%); (ii) NaOMe, methanol–THF (5 : 1), rt, 24 h, then (*R*)- or (*S*)-phenylglycinol, chlorobenzene, reflux, 24 h (79% of **2b**, 84% of **2c**).

We then turned our interest to the synthesis of pymox **2d**; the main structural distinction between pymox **2a** and **2d** being an inversion of the chiral appendage connecting the biaryl system (Scheme 6). By comparison of their performance in asymmetric catalytic cyclopropanation, we expected to gain insight into the individual contribution of both the chiral appendage and chiral biaryl axis on the enantioselective properties of this type of ligands. Ligand **2d** was prepared from the available 2-chloro-3-acetylpyridine **10**[13] and the boronic ester **11**[14] by a Suzuki coupling reaction, affording the cyclization precursor **12** in 98% yield. Lactamization of **12** upon heating at reflux in toluene with (*R*)-phenylglycinol proceeded smoothly, giving rise to the formation of the bicyclic lactam **13** in 64% yield as a single diastereoisomer. The synthesis of **2d** was then completed by oxazolidine construction at C-2 of the pyridine ring, following the classical sequence of *N*-oxidation (81%), Reissert reaction (58%) and oxazoline-ring formation (60%).



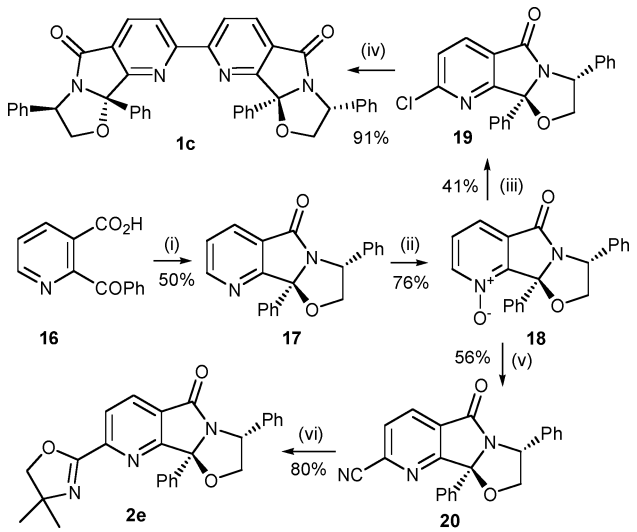
Scheme 6 Preparation of pymox **2d**. *Reagents and conditions*: (i) toluene, $Pd(PPh_3)_4$, EtOH, KOH, 60 °C, 4 h (98%); (ii) (*R*)-phenylglycinol, toluene, reflux, 2 days (64%); (iii) *m*-CPBA, CH_2Cl_2, rt, 72 h (81%); (iv) $(Me)_2NCOCl$, TMSCN, CH_2Cl_2, rt, 48 h (repeated twice) (58%); (v) $ZnCl_2$, 2-amino-2-methylpropanol, chlorobenzene, reflux, 48 h (60%).

Preparation of chiral analogues 1c and 2e devoid of stereogenic axis

Finally, in order to probe the role of the chiral biaryl axis on the performance of these ligands, the preparation of two analogues **1c** and **2e**,wherein the chiral biaryl axis is replaced by a stereogenic center, was undertaken. Ligands **1c** and **2e** were prepared in a similar manner to that developed for the preparation of their axially chiral analogues **1b** and **2a** by functionalization of the bicyclic lactam **17** (Scheme 7). The 5,5-fused bicyclic lactam **17** was obtained in 50% yield as a single diastereoisomer by lactamization of 2-benzoylpyridine 3-carboxylic acid **16** with (*R*)-phenylglycinol. Subsequent oxidation of **17** afforded pyridine *N*-oxide **18** in 76% yield, which was converted to 2-chloropyridine **19** in 41% yield. A homo-coupling reaction of **19** mediated by nickel in DMF at 60 °C afforded the C_2-symmetric 2,2′-bipyridine **1c** in 91% yield. From pyridine *N*-oxide **18**, pymox **2e** was obtained by a Reissert reaction (56%) followed by oxazoline formation (80%).

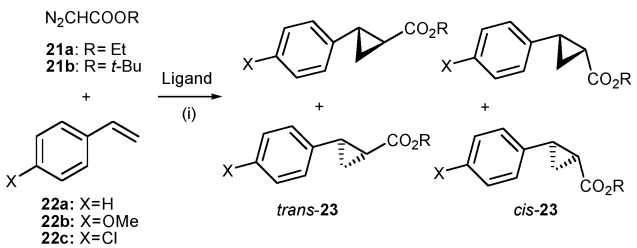
Evaluation of the ligands in catalytic asymmetric cyclopropanation

With 2,2′-bipyridyl ligands **1a–c** and pymox **2a–e** in hand, their evaluation in Cu(I)-catalyzed asymmetric cyclopropanation of styrene derivatives with diazoesters was undertaken. While the use of chiral 2,2′-bipyridine ligand in cyclopropanation is well documented,[1,15] chiral pymoxs have received less attention.[4a] This study was carried out under standard conditions using 1.2 mol% of the ligand and 1 mol% of copper(II) triflate in CH_2Cl_2 at room temperature. The standard procedure involves the slow addition of the diazoester by means of a syringe pump to the reaction mixture. Phenylhydrazine generates *in situ* the active copper(I) catalyst by reduction of the copper(II) triflate catalyst precursor. This reduction was accompanied by a change in color from light green to deep red, indicating the presence of the catalytically active species. Styrene, *p*-methoxystyrene and *p*-chlorostyrene derivatives **22a–c** were used to survey the influence of the electronic nature of



Scheme 7 Preparation of non-axially chiral 2,2′-bipyridine **1c** and pymox **2e** analogues. *Reagents and conditions*: (i) (*R*)-phenylglycinol, toluene, reflux, 48 h (50%); (ii) *m*-CPBA, CH_2Cl_2, rt, 72 h (76%) (iii) $POCl_3$, NEt_3, reflux, 12 h (41%); (iv) DMF, $NiCl_2$, $6H_2O$, Zn, PPh_3, 60 °C, 4 h (91%);(v) $(Me)_2NCOCl$, TMSCN, CH_2Cl_2, rt, 48 h (repeated twice) (56%); (vi) $ZnCl_2$, 2-amino-2-methylpropanol, chlorobenzene, reflux, 48 h (80%).

the *para*-substituent on the enantioselectivity of the cyclopropanation. The steric demand of the diazoester generally influences the *trans*/*cis* ratio, the *trans* isomer being obtained as major product when sterically hindered diazoesters are used. Ethyl and *t*-butyl diazoacetates **21a**,**b**, commonly employed as standard substrates in asymmetric cyclopropanation, were selected to evaluate these new ligands (Scheme 8).

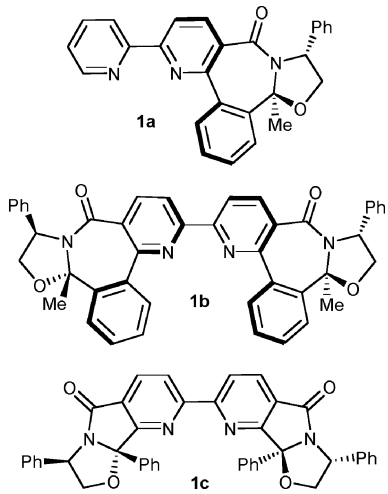


Scheme 8 Catalytic asymmetric cyclopropanation. *Reagents and conditions*: (i) CH_2Cl_2, rt, $PhNHNH_2$, $Cu(OTf)_2$.

Evaluation of 2,2′-bipyridyl ligands 1a–c

As can be seen from Table 1, cyclopropanes **23a–f** were obtained in fair to good yields (50–90%). In accordance with what is generally observed in the literature, the *trans*-isomer was obtained as the major product in all cases, however, with modest diastereoselectivities ranging from 60 : 40 to 78 : 22. As expected, the *trans*/*cis* selectivity was somewhat improved in favor of the *trans*-isomer by using the bulky *t*-butyl diazoacetate **21b**. The nature of the bipyridyl ligand **1a–c** has no significant effect on the *trans*/*cis* ratio. In contrast, the enantioselectivity was highly influenced by the nature of the ligands **1a–c** ranging from 0 to 65% ee. Ligand **1a** proved to be the most effective affording **23a–f** in 42% to 65% ee (Table 1, Entries 1–6). One can notice that the electronic nature of the *para*-substituent in styrenes **22a–c** exerts only a limited effect on both the diastereo-

Table 1 Catalytic asymmetric cyclopropanation of styrene derivatives **22** and diazoesters **21** with 2,2′-bipyridyl ligands **1a–c** and copper(I)



Entry	Ligand	Diazoester **21**	Styrene **22**	Yield (%)	Ratio[a] (*trans*/*cis*)	Ee[b] (*trans*/*cis*)
1	**1a**	**21a**	**22a**	67	**23a**, 60 : 40	57 : 46
2	**1a**	**21b**	**22a**	90	**23b**, 75 : 25	65 : 64
3	**1a**	**21a**	**22b**	75	**23c**, 62 : 38	nd : 42
4	**1a**	**21b**	**22b**	50	**23d**, 69 : 31	nd : 54
5	**1a**	**21a**	**22c**	68	**23e**, 64 : 36	nd : 52
6	**1a**	**21b**	**22c**	66	**23f**, 76 : 24	nd : 58
7	**1b**	**21a**	**22a**	84	**23a**, 66 : 34	26 : 10
8	**1b**	**21b**	**22a**	64	**23b**, 75 : 25	31 : 14
9	**1b**	**21a**	**22b**	80	**23c**, 60 : 40	nd : 6
10	**1b**	**21b**	**22b**	75	**23d**, 73 : 27	nd : 20
11	**1b**	**21a**	**22c**	87	**23e**, 62 : 38	nd : 17
12	**1b**	**21b**	**22c**	65	**23f**, 78 : 22	nd : 13
13	**1c**	**21b**	**22a**	65	**23b**, 72 : 28	15 : 0

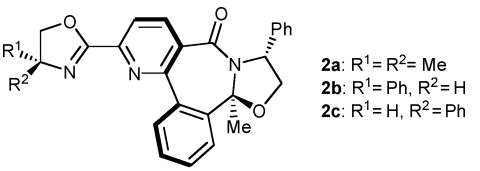
[a] Determined by GC. [b] Enantiomers of the *trans*-cyclopropanes **23c–f** reaction products could not be separated by chiral GC (Chiraldex CB 25 m × 0.25 mm).

and enantioselectivity of the reaction (Table 1, Entries 1, 3 and 5). The C_2-symmetric 2,2′-bipyridyl ligand **1b** furnished **23a–f** in much lower enantioselectivity (up to 31%) (Table 1, Entries 7–12). This result is surprizing in that it has been frequently shown that C_2-symmetric bipyridyl ligands are capable of providing high ee's.[15] Additionally, when compared with C_1-symmetric bipyridyl analogues, it is apparent that C_2-symmetric bipyridyl ligands usually give rise to higher levels of enantioselection.[15f] In our case, although its efficiency remains rather modest, the C_1-symmetric bipyridyl ligand **1a** turned out to be more efficient than the C_2-symmetric ligand **1b**. Interestingly, the incapability of ligand **1c** to induce a substantial enantioselectivity during cyclopropanation of styrene **22a** with *t*-butyl diazoacetate **21b** seems to designate the chiral biaryl axis as an important element of chirality in the design of these ligands (Table 1, Entry 13).

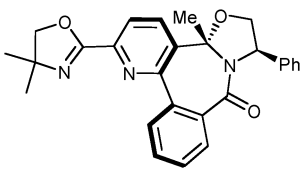
Evaluation of pymox ligands 2a–e

As can be seen from Table 2, pymox **2a–e** showed mostly similar trends to those observed with bipyridyl ligands **1a–c** in terms of yields (49–100%) and *trans*/*cis* selectivities (56 : 44 to 77 : 23). Although the enantioselective performances of pymox **2a** remain moderate (up to 52% ee), these results are similar to those obtained with previously reported pymox.[4a] The effect of an additional stereogenic center at the oxazoline moities of pymox **2b–c** was then

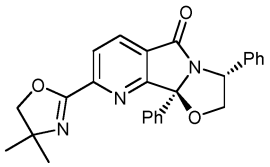
Table 2 Catalytic asymmetric cyclopropanation of styrene derivatives **22** and diazoesters **21** with pymox ligands **2a–e** and copper(I)



2a: $R^1 = R^2 = Me$
2b: $R^1 = Ph$, $R^2 = H$
2c: $R^1 = H$, $R^2 = Ph$



2d



2e

Entry	Ligand	Diazoester **21**	Styrene **22**	Yield (%)	Ratio[a] (*trans*/*cis*)	Ee[b] (*trans*/*cis*)
1	**2a**	**21a**	**22a**	62	**23a**: 64 : 36	46 : 40
2	**2a**	**21b**	**22a**	80	**23b**: 72 : 28	52 : 44
3	**2a**	**21a**	**22b**	82	**23c**: 62 : 38	nd : 42
4	**2a**	**21b**	**22b**	77	**23d**: 67 : 33	nd : 44
5	**2a**	**21a**	**22c**	96	**23e**: 56 : 44	nd : 44
6	**2a**	**21b**	**22c**	71	**23f**: 77 : 23	nd : 40
7	**2b**	**21b**	**22a**	74	**23b**: 61 : 39	53 : 32
8	**2c**	**21b**	**22a**	85	**23b**: 72 : 38	7 : 5
9	**2d**	**21a**	**22a**	100	**23a**: 64 : 36	46 : 47
10	**2d**	**21b**	**22a**	90	**23b**: 71 : 29	50 : 40
11	**2d**	**21a**	**22b**	83	**23c**: 62 : 38	nd : 44
12	**2d**	**21b**	**22b**	64	**23d**: 70 : 30	nd : 39
13	**2d**	**21a**:	**22c**	66	**23e**: 64 : 36	nd : 48
14	**2d**	**21b**	**22c**	49	**23f**: 77 : 23	nd : 45
15	**2e**	**21b**	**22a**	94	**23b**: 76 : 24	0 : 0

[a] Determined by GC. [b] Enantiomers of the *trans*-cyclopropanes **23d–f** reaction products could not be separated by chiral GC (Chiraldex CB 25 m × 0.25 mm).

investigated. While the performance of pymox **2b** proved comparable to that of **2a** (Table 2, Entries 2 and 7), the performance of pymox **2c** was drastically affected by the presence of this additional chiral element (Table 2, entries 2 and 8). Thus, whereas a mismatch effect was observed with (*S*)-phenylglycinol, no assistance of a match effect, that would have improved the enantioselectivity, was recorded with (*R*)-phenylglycinol. Comparison of the results obtained with pymox **2a** and **2d** indicates that an inversion of the chiral lactam appendage linking the biaryl system has only a limited effect on the enantio- and diastereoselective outcome of the reaction (Table 2, Entries 1–6, 9–14). This may be explained by the fact that the chiral appendage is too far from the catalytic site to influence the stereochemical course of the reaction. Thus, it could be concluded from these results that in both pymox **2a** and **2d**, the chiral biaryl axis is the main element of chirality responsible for the stereochemical outcome of the cyclopropanation. As earlier observed for the 2,2′-bipyridyl ligands series, the replacement of this chiral axis with a stereogenic center in pymox **2e** provokes a disastrous effect on the enantioselective properties of the ligand (Table 2, Entry 15).

Conclusions

The synthesis of new axially chiral biaryl *N*,*N*-ligands in 2,2′-bipyridyl and pymox series has been developed. Their preparation is essentially based on an atroposelective lactamization of keto-ester biaryl systems and subsequent functionalization of the resulting 7,5-fused bicyclic lactam **3**. By this modular approach, ligands were obtained in three to five steps from lactam **3** and could be prepared on a multi-gram scale. A preliminary evaluation of these bidentate *N*,*N*-ligands has been investigated in catalytic asymmetric cyclopropanation. Whereas 2,2′-bipyridyl ligands **1** afforded cypropropanes **23** in up to 65% ee, enantioselectivities did not exceed 53% ee with pymox ligands **2**. Diverse modular modifications of the ligands gave some evidence that, among the multiple elements of chirality present in the structure, the chiral biaryl axis plays a crucial role in their enantioselective properties. The potential of these bidentate ligands is presently being evaluated for other catalytic asymmetric processes.

Experimental

General methods

Chemicals were purchased and used without further purification. ^{1}H and ^{13}C were recorded on a Bruker Avance 300 with chloroform-d_1 (δ 7.26, ^{1}H; δ 77.0, ^{13}C) as internal standard unless otherwise indicated. Melting points were determined on a Kofler block. Optical rotations were recorded in CH_2Cl_2. The $[\alpha]_D$ values are given in 10^{-1}deg cm^{-3} g^{-1}. The IR spectra were recorded on a Perkin Elmer Paragon 500. Elemental analyses were performed by the University of Rouen Microanalytical Service Laboratory on a Carlo Erba 1160. Mass spectrometry was performed by the University of Rouen Spectroscopy Center. Electron impact (EI) and chemical ionization (IC) spectra were performed on a Jeol JMS AX-500 spectrometer. Routine monitoring of the reaction was performed by TLC, using 0.2 Kieselgel 60 F_{254} precoated aluminium sheets, commercially available from Merck. Flash chromatography was performed on Gerudan SI-60 (70–230 mesh ASTM) from Merck. Tetrahydrofuran (THF) was distilled on sodium benzophenone ketyl under nitrogen. The following compounds were prepared according literature methods: lactam **3**;[5] 2-(tributylstannyl)pyridine;[7] 2-chloro-3-acetylpyridine **10**;[13] and boronic ester **11**.[14]

***Trans*-(3*R*,13b*S*,a*S*)-methyl-3-phenyl-2,3-dihydro-13b*H*-benz-[c]oxazolo[3,2-a]-*N*-oxide-pyrido[2,3-e]azepin-5-one (4).** To a solution of lactam **3** (700 mg, 2.04 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (70%, 1.51 g, 6.13 mmol). The mixture was stirred for 48 hours at room temperature. A cold 40% aqueous NaOH solution (2 mL) was added, and this suspension was stirred for a further 1 hour at room temperature. Water (10 mL) and dichloromethane (10 mL) were added. The organic layer was separated, dried with magnesium sulfate, filtered and solvents were removed to afford a pale yellow oil. Flash chromatography on silica gel of the residue (eluent used was EtOAc–cyclohexane 95 : 5) provided (3*R*,13b*S*,a*S*)-**4** (530 mg, 72%) as a white solid. Mp 110 °C. ^{1}H NMR 300 MHz, ($CDCl_3$) δ 8.47 (d, J = 6.1 Hz, 1H), 8.40 (dd, J = 8.6 and 1.1 Hz, 1H), 7.73–7.67 (m, 2H), 7.54–7.29 (m, 8H), 5.43 (d, J = 6.0 Hz, 1H), 4.42 (dd, J = 6.4 and 2.0 Hz, 1H), 4.33 (dd, J = 8.7 and 1.0 Hz, 1H), 1.69 (s, 3H). ^{13}C NMR

75 MHz, ($CDCl_3$) δ 161.5, 145.3, 143.0, 142.5, 140.4, 134.4, 132.6, 131.0, 129.2 (2 C), 128.3, 127.8, 127.4 (2 C), 125.8, 124.9, 122.6, 94.3, 71.4, 61.8, 26.9. IR υ_{max} cm^{-1} (KBr): 1643, 1428, 1395, 1247, 1217, 1037, 747, 700. Anal. Calc. for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.82; H, 5.13; N, 7.81. $[\alpha]_D^{20} = -83.66$ ($c = 3.55$, CH_2Cl_2).

***Trans*-(3*R*,13b*S*,a*S*)-13b-methyl-3-phenyl-2,3-dihydro-13b*H*-benz[c]oxazolo[3,2-a](6-chloropyrido)[2,3-e]azepin-5-one (5a).** To a solution of dry *N*-oxide **4** (200 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) were added triethylamine (94 μL, 0.67 mmol) and phosphorus oxychloride (62 μL, 67 mmol). The mixture was stirred for 30 min, refluxed for 1 hour and then cooled to room temperature. The solution was neutralized with a 2M NaOH aqueous solution. After phase separation, the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and solvent was evaporated under vacuum. Flash chromatography of the residue on silica gel (eluent used was EtOAc–cyclohexane 1 : 9) provided 2-chloropyridine **5a** (63 mg, 30%) and 4-chloropyridine **5b** (36 mg, 20%). Compound **5a** was obtained as a white solid. Mp 82 °C. ^{1}H NMR 300 MHz, ($CDCl_3$) δ 8.07 (d, $J = 7.9$ Hz, 1H), 8.02 (m, 1H), 7.60 (m, 1H), 7.45 (m, 4H), 7.17–7.34 (m, 4H), 5.32 (d, $J = 5.6$ Hz, 1H), 4.34 (dd, $J = 8.7$ Hz and 6.0 Hz, 1H), 4.23 (d, $J = 8.7$ Hz, 1H), 1.54 (s, 3H). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 162.7, 154.3, 153.8, 142.3, 142.2, 140.7, 134.4, 132.3, 130.8, 129.4, 129.1, 128.6, 128.3, 127.5, 123.8, 122.6, 94.1, 71.4, 62.5, 27.3. IR υ_{max} cm^{-1} (KBr): 1635, 1571, 1409, 1183, 1092, 764, 698. Anal. Calc. for $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 7.43. Found: C, 70.25; H, 4.58; N, 7.48. $[\alpha]_D^{20} = +48.1$ ($c = 0.77$, CH_2Cl_2). Compound **5b** was obtained as a white solid. Mp 68 °C. ^{1}H NMR 300 MHz, ($CDCl_3$) δ 8.59 (d, $J = 8.0$ Hz, 1H), 8.03 (m, 1H), 7.57 (m, 1H), 7.18–7.46 (m, 8H), 5.49 (d, $J = 6.4$ Hz, 1H), 4.39 (dd, $J =$ 6.8 Hz and 9.0 Hz, 1H), 4.22 (dd, $J = 9.0$ Hz and 1.1 Hz, 1H), 1.50 (s, 3H). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 160.8, 155.0 151.4, 144.6, 142.9, 140.61 135.3, 131.9, 130.5, 129.4, 129.1, 129.0, 128.1, 126.6, 124.7, 122.8, 94.6, 71.5, 61.0, 26.7. IR υ_{max} cm^{-1} (KBr): 2924, 2361, 1645, 1384, 1038, 758. Anal. Calc. for $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 7.43. Found: C, 69.94; H, 4.38; N, 7.51. $[\alpha]_D^{20} = -16.7$ ($c =$ 0.12, CH_2Cl_2).

***Trans*-(3*R*,13b*S*,a*S*)-13b-methyl-3-phenyl-2,3-dihydro-13b*H*-benz[c]oxazolo[3,2-a]-6-(2-pyridyl)pyrido[2,3-e]azepin-5-one (1a).**

*By Stille cross-coupling reaction of 2-chloropyridine **5a** with 2-(tributylstannyl)pyridine.* To a solution of 2-chloropyridine **5a** (752 mg, 2 mmol) and 2-(tributylstannyl)pyridine (736 mg, 2 mmol) in toluene (15 mL) was added $Pd[(PPh_3)]_4$ (0.167 g, 0.136 mmol). The resulting solution was refluxed for 24 h, after which the solution was filtered and evaporated under vacuum to afford a brown solid. The residue was purified by flash chromatography on silica gel (eluent used was EtOAc–cyclohexane 1 : 5) to give ligand **1a** (250 mg, 30%) as a white solid. Mp 216 °C. ^{1}H NMR 300 MHz, ($CDCl_3$) δ 8.65 (d, $J = 4.9$ Hz, 1H), 8.56 (d, $J = 7.8$ Hz, 1H), 8.45 (d, $J = 8.3$ Hz, 1H), 8.28 (d, $J = 8.3$ Hz, 1H), 8.2 (m, 1H), 7.80 (dt, $J = 7.9$ and 1.5 Hz, 1H), 7.65 (m, 1H), 7.50 (m, 4H), 7.30 (m, 4H), 5.40 (d, $J = 8.9$ Hz, 1H), 4.40 (d, $J = 8.9$ Hz, 1H), 4.25 (d, $J = 8.9$ Hz, 1H), 1.60 (s, 3H). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 163.7, 158.1, 155.6, 152.9, 149.7, 142.3, 140.9, 140.4, 137.4, 136.0, 132.2, 130.2, 129.6, 129.2, 129.1, 128.1, 127.5, 124.9, 122.5, 122.2, 120.1, 94.2, 71.4, 62.4, 27.3. IR υ_{max} cm^{-1} (KBr): 2887, 1635, 1408. HRMS IC calc. for $C_{27}H_{22}N_3O_2$: $m/z =$ 420.1712. Found: $(MH)^+$ $m/z = 420.1704$.

*By atroposelective lactamization of keto-ester **8** with (R)-phenylglycinol.* Keto-ester **8** (1.56 g, 4.5 mmol) and (*R*)-phenylglycinol (617 mg, 4.5 mmol) were dissolved in toluene (50 mL) in a Dean–Stark apparatus. The mixture was stirred at reflux for 6 days and then cooled to room temperature. Toluene was removed under vacuum, flash chromatography of the residue (eluent used was EtOAc–CH_2Cl_2–cylohexane 2 : 7 : 1) provided ligand **1a** (1.80 g, 60%) as a white solid.

*By Co-cyclotrimerization of acetylene and cyanopyridine **9**.* A thermostated (25 °C) reaction vessel, equipped with a very effective quill spin bar, was loaded with 500 mg (1.36 mmol) of 2-cyanopyridine **9** and 2.7 mg (0.011 mmol) of CpCo(cod). Toluene (10 mL) was added to the mixture, and the vessel was connected to an acetylene delivering and measuring device providing a constant pressure of acetylene. Alternatively, acetylene may simply be bubbled through the solution. The mixture was irradiated by two 460 W Phillips HPM-12 lamps (420 nm) for 5 h. The reaction was quenched by switching off the lamps and simultaneously introducing air. The obtained reaction mixture was filtered and chromatographed on silica gel (eluent used was toluene–EtOAc 5 : 1) to give ligand **1a** (456 mg, 80%) as a white solid.

6,6′-Bis(*trans*-(3*R*,13b*S*,a*S*)-13b-methyl-3-phenyl-2,3-dihydro-13b*H*-benz[c]oxazolo[3,2-a]pyrido[2,3-e]azepin-5-one (1b). To a stirred solution of nickel(II) chloride hexahydrate (64 mg, 0.27 mmol) and triphenylphosphine (283 mg, 1.08 mmol) in dry, degassed DMF (1 mL) was added zinc dust (<10 μm, 23 mg, 0.35 mmol). The resulting suspension was heated at 60 °C for 1 hour. A solution of 2-chloropyridine **5a** (100 mg, 0.27 mmol) in dry, degassed DMF (1 mL) was then added. The resultant mixture was heated at 60 °C for 4 hours. The reaction mixture was then allowed to cool to room temperature and was poured into 10% aqueous ammonium hydroxide (50 mL). The resultant mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography of the residue on silica gel (eluent used was EtOAc–cyclohexane 1 : 4) provided ligand **1b** (55 mg, 61%) as a white powder. Mp 312 °C. ^{1}H NMR 300 MHz, ($CDCl_3$) δ 8.70 (d, $J = 8.3$ Hz, 2H), 8.36 (d, $J = 8.3$ Hz, 2H), 8.31 (dd, $J =$ 1.9 Hz and 7.5 Hz, 2H), 7.72 (dd, $J = 7.5$ Hz and 1.5 Hz, 2H), 7.53–7.66 (m, 8H), 7.30–7.45 (m, 6H), 5.45 (d, $J = 5.6$ Hz, 2H), 4.47 (dd, $J = 8.7$ Hz and 6.0 Hz, 2H), 4.33 (d, $J = 8.6$ Hz, 2H), 1.62 (s, 6H). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 163.6, 157.3, 153.2, 142.3, 141.0, 140.6, 135.8, 132.4, 130.4, 130.2, 129.3, 129.1, 128.2, 127.6, 122.6, 120.9, 94.2, 62.5, 27.4. IR υ_{max} cm^{-1} (KBr): 2367, 1637, 1406, 1037, 696. Anal. Calcd. for $C_{44}H_{34}N_4O_4$: C, 77.40; H, 5.02; N, 8.21. Found: C, 77.24; H, 5.17; N, 8.16. $[\alpha]_D^{20} = -51.4$ ($c = 1.09$, CH_2Cl_2).

6-Chloro-2,2′-bipyridine (6). To a solution of 2,6-dichloropyridine (6.03 g, 40.76 mmol) and 2-(tributylstannyl)-pyridine (5 g, 13.58 mmol) in degassed toluene (50 mL) was added $Pd[(PPh_3)]_4$ (0.784 g, 0.679 mmol). The resulting solution was refluxed for 24 h under nitrogen, after which the solution was filtered and evaporated under vacuum to afford a brown solid. The residue was purified by flash chromatography on silica gel (eluent used was EtOAc–cyclohexane 1 : 5) to give 2,2′-bipyridine **6** (1.78 g, 69%) as a white solid. Mp 62 °C. ^{1}H NMR 300 MHz,

($CDCl_3$) δ 8.57 (d, $J = 4.1$ Hz, 1H), 8.30 (d, $J = 7.9$ Hz, 1H), 8.25 (d, $J = 7.9$ Hz, 1H), 7.72 (t, $J = 4.1$ Hz, 1H), 7.67 (t, $J = 7.9$ Hz, 1H), 7.24–7.20 (m, 2H). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 157.2, 154.9, 151.3, 149.6, 139.9, 124.65, 124.6, 121.8, 119.8. IR υ_{max} cm^{-1} (KBr): 3061, 1583, 1427, 1135. Anal. Calc. for $C_{10}H_7ClN_2$: C, 63.01; H, 3.70; N, 14.70. Found: C, 63.03; H, 3.74; N, 14.66.

6-Chloro-2,2′-bipyridine-5-carboxylic acid ethyl ester (7). To a solution of diisopropylamine (156 mg, 1.54 mmol) in dry THF (3 mL) was added under nitrogen at 0 °C a solution of butyllithium in hexanes (0.62 mL, 2.5 M, 1.54 mmol). The resulting solution was stirred for 15 min before being added to a solution of 2,2′-bipyridine **6** (100 mg, 0.516 mmol) in THF (3 mL) at −78 °C. The solution was stirred at this temperature for 1 h, after which a solution of ethyl cyanoformate (205 mg, 2.06 mmol) in dry THF (8 mL) was added. After being stirred for 2 h at −78 °C, the solution was quenched with water (10 mL). After phase separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated under vacuum. The resulting brown solid was recrystallized from methanol–water (1 : 1) to afford white crystals (83 mg, 65%). Mp 98 °C. ^{1}H NMR 300 MHz, ($CDCl_3$) δ 8.62 (d, $J = 4.5$ Hz, 1H), 8.40–8.34 (m, 2H), 8.21 (d, $J = 7.9$ Hz, 1H), 7.77 (t, $J = 7.9$ Hz, 1H), 7.30 (t, $J = 4.5$ Hz, 1H), 4.38 (q, $J = 7.2$ Hz, 2H), 1.37 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 165.0, 158.8, 154.0, 149.8, 141.65, 137.5, 125.3, 122.5, 119.4, 62.4, 14.6. IR υ_{max} cm^{-1} (KBr): 3050, 1731, 1585, 1435, 1151. Anal. Calc. for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66. Found: C, 59.42; H, 4.15; N, 10.54.

6-(2-Acetylphenyl)-2,2′-bipyridine-5-carboxylic acid ethyl ester (8). To a solution of 2,2′-bipyridine **7** (150 mg, 0.57 mmol) in toluene (15 mL) and ethanol (1.2 mL), 2-acetylphenylboronic acid (103 mg, 0.63 mmol) and K_2CO_3 aqueous solution (0.414 g in 1.5 mL of water) were added. The mixture was degassed under a N_2 flow for 30 min. After adding $Pd[(PPh_3)]_4$ (58 mg, 5%) the mixture was degassed under a N_2 flow for a further 15 min. The mixture was stirred at reflux under an inert atmosphere for 48 h, cooled to room temperature and filtered through a plug of celite. Toluene was removed, Et_2O (100 mL) was added and the organic layer was extracted with water (50 mL). After drying over $MgSO_4$, the solvents were removed under vacuum, and the residue was purified by flash chromatography (eluent used was EtOAc–cyclohexane 1 : 1) to afford **8** (130 mg, 66%) as a yellow oil. ^{1}H NMR 300 MHz, ($CDCl_3$) δ 8.60 (d, $J = 4.2$ Hz, 1H), 8.40 (d, $J = 8.3$ Hz, 1H), 8.28 (m, 2H), 7.70 (m, 2H), 7.43 (m, 2H), 7.22 (m, 2H), 4.08 (q, $J = 7.2$ Hz, 2H), 2.18 (s, 3H), 1.00 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 201.6, 166.8, 159.8, 155.2, 149.6, 141.2, 137.5, 124.8, 122.5, 119.4, 61.7, 30.1, 14.6. Anal. Calc. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.77; H, 5.30; N, 8.06.

***Trans*-(3*R*,13b*S*,a*S*)-13b-methyl-3-phenyl-2,3-dihydro-13b*H*-benz[c]oxazolo[3,2-a](6-cyanopyrido)[2,3-e]azepin-5-one (9) (procedure A).** To a solution of *N*-oxide **4** (200 mg, 0.56 mmol) in CH_2Cl_2 (2 mL) was added trimethylsilyl cyanide (61 mg, 0.61 mmol) and dimethylcarbamoyl chloride (53 µL, 0.55 mmol). The mixture was stirred at room temperature for 2 days, after which the same amount of dimethylcarbamoyl chloride and cyanotrimethylsilane were added and the solution was allowed to stir for a further 2 days. The mixture was treated with a 10% K_2CO_3 aqueous solution. After phase separation, the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined dichloromethane layers were dried ($MgSO_4$) and rotary evaporated. Flash chromatography of the residue (eluent used was EtOAc–cyclohexane 1 : 1) provided **9** as a white solid (198 mg, 97%). Mp 91 °C. ^{1}H NMR 300 MHz, ($CDCl_3$) δ 8.20 (d, $J = 7.9$ Hz, 1H), 8.02 (m, 1H), 7.60 (m, 2H), 7.44 (m, 4H), 7.25 (m, 3H), 5.31 (d, $J = 5.7$ Hz, 1H), 4.33 (dd, $J = 9.0$ Hz and 6.0 Hz, 1H), 4.22 (d, $J = 9.0$ Hz, 1H), 1.48 (s, 3H). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 161.4, 154.5, 141.8, 140.2, 139.8, 135.2, 133.4, 131.9, 130.7, 129.0, 128.6, 127.8, 126.9, 126.6, 122.2, 116.5, 93.4, 70.9, 62.0, 27.0. IR υ_{max} cm^{-1} (KBr): 1640, 1416, 1240, 1037, 765, 699. Anal. Calc. for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44. Found: C, 75.26; H, 4.65; N, 11.26. $[\alpha]_D^{20} = +35.9$ ($c = 0.39$, CH_2Cl_2).

***Trans*-(3*R*,13b*S*,a*S*)-13b-methyl-3-phenyl-2,3-dihydro-13b*H*-benz[c]oxazolo[3,2-a](6-(4,5-dihydro-4,4-dimethyloxazol-2-yl))-pyrido[2,3-e]azepin-5-one (2a) (procedure B).** To a solution of dry $ZnCl_2$ (5.6 mg, 0.04 mmol) in chlorobenzene (5 mL) was added under nitrogen cyanopyridine **9** (150 mg, 0.41 mmol) and 2-amino-2-methylpropanol (40 mg, 0.45 mmol). The mixture was refluxed for 2 days under nitrogen and then cooled to room temperature. Water (10 mL) was added. After phase separation, the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The organic phase was dried ($MgSO_4$) and the solvent evaporated under vacuum. Flash chromatography on silica gel (eluent used was EtOAc–cyclohexane 3 : 7) furnished ligand **2a** as a white powder (162 mg, 90%). Mp 95 °C. ^{1}H NMR 300 MHz, ($CDCl_3$) δ 8.29 (d, $J = 1.9$ Hz, 1H), 8.13–8.17 (m, 2H), 7.65 (m, 1H), 7.50–7.56 (m, 4H), 7.32–7.42 (m, 3H), 5.43 (d, $J = 5.6$ Hz, 1H), 4.44 (dd, $J = 8.6$ Hz and 4.0 Hz, 1H), 4.32 (d, $J = 8.7$ Hz, 1H), 4.25 (s, 2H), 1.58 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 163.1, 161.2, 153.7, 149.3, 142.1, 140.7, 140.0, 135.4, 132.6, 131.1, 130.3, 129.5, 129.1, 128.2, 127.5, 123.1, 122.3, 94.2, 80.2, 71.4, 68.6, 62.4, 30.6, 28.8, 27.3. IR υ_{max} cm^{-1} (KBr): 1638, 1415, 1364, 1086, 733. Anal. Calc. for $C_{27}H_{25}N_3O_3$: C, 73.78; H, 5.73; N, 9.56. Found: C, 73.83; H, 5.80; N, 9.45. $[\alpha]_D^{20} = +15.8$ ($c = 0.38$, CH_2Cl_2).

***Trans*-(3*R*,13b*S*,a*S*)-13b-methyl-3-phenyl-2,3-dihydro-13b*H*-benz[c]oxazolo[3,2-a]-6-[(*R*)-4,5-dihydro-4-phenyloxazol-2-yl]-[2,3-e]azepin-5-one (2b) (procedure C).** To a solution of methanol–THF (6 mL, 5 : 1) was added cyanopyridine **9** (200 mg, 0.54 mmol) and sodium methylate (8.8 mg, 0.16 mmol). The mixture was stirred at room temperature for one day. Water (10 mL) was added and after phase separation, the aqueous phase was extracted with CH_2Cl_2 (15 mL). The organic solvents were evaporated under vacuum. To the resulting residue was added (*R*)-phenylglycinol (164 mg, 1.2 mmol) and chlorobenzene (10 mL) and the mixture was refluxed for 24 hours. After evaporation of the solvent, flash chromatography of the crude product (eluent used was cyclohexane–EtOAc 7 : 3) provided ligand **2b** (210 mg, 79%) as a white solid. Mp 94 °C. ^{1}H NMR 300 MHz, ($CDCl_3$) δ 8.34–8.19 (m, 3H), 7.68 (m, 1H), 7.57–7.51 (m, 4H), 7.43–7.29 (m, 8H), 5.53–5.44 (m, 2H), 4.94 (dd, $J = 10.4$ and 8.7 Hz, 1H), 4.46 (m, 2H), 4.34 (dd, $J = 10.9$ and 0.8 Hz, 1H), 3.10 (s, 3H). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 163.9, 163.1, 153.8, 148.9, 142.2, 142.0, 140.7, 140.2, 135.3, 132.5, 131.4, 130.4, 129.6, 129.3, 129.1, 128.3, 128.2, 127.5, 127.3, 123.4, 122.4, 94.2, 76.0, 71.4, 70.9, 62.4, 27.4. IR υ_{max} cm^{-1} (KBr): 2926, 1638, 1417, 1367. HRMS calc. for

$C_{31}H_{26}N_3O_3$ [MH+]: 488.1973, found: 488.1973. $[\alpha]_D^{20} = +60.6$ (c = 1.04, CH_2Cl_2).

***Trans*-(3*R*,13b*S*,a*S*)-13b-methyl-3-phenyl-2,3-dihydro-13b*H*-benz[c]oxazolo[3,2-a]-6-[(*S*)-4,5-dihydro-4-phenyloxazol-2-yl]-[2,3-e]azepin-5-one (2c).** Prepared as described for **2b** according to procedure C from cyanopyridine **9** (200.0 mg, 0.54 mmol) and (*S*)-phenylglycinol (82.2 mg, 0.60 mmol). Flash chromatography (eluent used was EtOAc–cyclohexane 3 : 7) of the crude product afforded ligand **2c** (223 mg, 84%) as a white solid. Mp 106 °C. ^{1}H NMR 300 MHz, ($CDCl_3$) δ 8.34–8.19 (m, 3H), 7.67 (m, 1H), 7.57 (m, 4H), 7.43–7.30 (m, 8H), 5.51 (dd, J = 10.1 and 9.0 Hz, 1H), 5.45 (d, J = 6.0 Hz, 1H), 4.96 (dd, J = 10.3 and 8.9 Hz, 1H), 4.48–4.40 (m, 2H), 4.33 (d, J = 8.7 Hz, 1H), 1.62, (s, 3H). ^{13}C NMR 75 MHz, ($CDCl_3$) δ 163.8, 163.1, 153.8, 148.9, 142.2, 142.0, 140.7, 140.2, 135.3, 132.5, 131.4, 130.4, 129.6, 129.3, 129.1, 128.3, 128.2, 127.5, 127.3, 123.4, 122.4, 94.2, 76.0, 71.4, 70.9, 62.5, 27.4. IR υ_{max} cm^{-1} (KBr): 2924, 2851, 1635, 1416, 1366. Calcd. for $C_{31}H_{25}N_3O_3$: C, 76.37; H, 5.17; N, 8.62. Found: C, 76.30; H, 5.29; N, 8.54. $[\alpha]_D^{20} = -28.6$ (c = 0.28, CH_2Cl_2).

General procedure for asymmetric cyclopropanation catalyzed by ligand–Cu(I) complexes. A solution of the ligand (0.03 mmol) and $Cu(TfO)_2$ (9 mg, 0.025 mmol) in CH_2Cl_2 (1 mL) was stirred under a nitrogen atmosphere at 20 °C for 1 hour. Phenylhydrazine (3 μL, 0.03 mmol) was then added, and the color of the solution changed from light green to deep red. After 10 min, alkene (4.37 mmol) was added. A solution of the corresponding diazoester (ethyldiazoacetate or *t*-butyldiazoacetate) (2.5 mmol) in dry CH_2Cl_2 was added over *ca.* 5 hours *via* a syringe pump. After the addition was complete, the reaction was stirred for an additional 12 h. The reaction was then concentrated *in vacuo* to afford the crude product. Conversion was determined by ^{1}H NMR. Flash chromatography of the residue (Eluent used was EtOAc–cyclohexane 1 : 24) provided a mixture of *trans*/*cis* isomers. The *trans*/*cis* ratio and enantiomeric excess of each isomer were determined by chiral GC (Chiraldex CB 25 m × 0.25 mm) after filtration on silica gel.

Acknowledgements

We thank the CNRS, the région Haute-Normandie and the CRIHAN for financial and technical support. A. B. thanks the MRT for a grant.

Notes and references

1 For reviews on the preparation and applications in asymmetric catalytic synthesis of 2,2′-bipyridyl ligands, see: (*a*) N. C. Fletcher, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1831; (*b*) G. Chelucci and R. P. Thummel, *Chem. Rev.*, 2002, **102**, 3129.
2 C. Botteghi, A. Schionato and O. De Lucchi, *Synth. Commun.*, 1991, **21**, 1819.
3 T. Shimada, A. Kina and T. Hayashi, *J. Org. Chem.*, 2003, **68**, 6329.
4 For recent investigations of pymox ligands in asymmetric catalytic processes, see: (*a*) G. Chelucci, M. G. Sanna and S. Gladiali, *Tetrahedron*, 2000, **56**, 2889; (*b*) W. Xu, A. Kong and X. Lu, *J. Org. Chem.*, 2006, **71**, 3854; (*c*) D. W. Dodd, H. E. Toews, F. D. S. Carneiro, M. C. Jennings and N. D. Jones, *Inorg. Chim. Acta*, 2006, **359**, 2850; (*d*) H. Brunner, H. B. Kagan and G. Kreutzer, *Tetrahedron: Asymmetry*, 2003, **14**, 2177; (*e*) Q. Zhang, X. Lu and X. Han, *J. Org. Chem.*, 2001, **66**, 7676; (*f*) H. Brunner, R. Störiko and F. Rominger, *Eur. J. Inorg. Chem.*, 1998, **6**, 771.
5 M. Penhoat, V. Levacher and G. Dupas, *J. Org. Chem.*, 2003, **68**, 9517.
6 (*a*) A. Ohno, A. Tsutsumi, N. Yamazaki, M. Okamura, Y. Mikata and M. Fujii, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1679; (*b*) M. Iyoda, H. Otsuka, K. Sato, N. Nisato and M. Oda, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 80; (*c*) M. F. Semmelhack, P. Helquist, L. D. Jones, L. Keller, L. Mendelson, L. Speltz Ryono, J. Gorzynski, Smith and R. D. Stauffer, *J. Am. Chem. Soc.*, 1981, **103**, 6460.
7 H. Nierengarten, J. Rojo, E. Leize, J.-M. Lehn and A. Van Dorsselaer, *Eur. J. Inorg. Chem.*, 2002, **3**, 573.
8 B. Heller, B. Sundermann, H. Buschmann, H.-J. Drexler, J. You, U. Holzgrabe, E. Heller and G. Oehme, *J. Org. Chem.*, 2002, **67**, 4414.
9 H. Bönnemann and W. Brijoux, *Aspects Homogeneous Catal.*, 1984, **5**, 75.
10 Crystal, X-ray data collection and refinement parameters for **1a**‡. Formula: $C_{27}H_{21}N_3O_2$; chemical formula weight: 419.47 g mol^{-1}; crystal system: orthorhombic; space group: $P2_12_12_1$; unit-cell dimensions: a = 10.052(2) Å, b = 15.052(3) Å, c = 42.205(8) Å, V = 6386(2) Å^3; T (K) = rt; Z' = 3; $F(000)$ = 2640 e$^-$; μ = 0.084 mm^{-1}; number of independent reflexions : 8869; R_{int} = 0.0339, R_1 = 0.0684 & wR_2 = 0.1820 for 6491 reflections with $I > 2\sigma I$.
11 (*a*) C. Bolm, K. Weickhardt, M. Zehnder and T. Ranff, *Chem. Ber.*, 1991, **124**, 1173; (*b*) K. M. Button, R. A. Gossage and R. K. R. Phillips, *Synth. Commun.*, 2002, **32**, 363.
12 V. K. Aggarwal, L. Bell, M. P. Coogan and P. Jubault, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2037.
13 A. D. Dunn and R. Norrie, *Z. Chem.*, 1990, **30**, 245.
14 F. Hof, M. Schär, D. M. Scofield, F. Fischer, F. Diederich and S. Sergeyev, *Helv. Chim. Acta*, 2005, **88**, 2333.
15 (*a*) K. Ito and T. Katsuki, *Tetrahedron Lett.*, 1993, **34**, 2661; (*b*) M. P. A. Lyle and P. D. Wilson, *Org. Lett.*, 2004, **6**, 855; (*c*) M. P. A. Lyle, N. D. Draper and P. D. Wilson, *Org. Biomol. Chem.*, 2006, **4**, 877; (*d*) H.-L. Kwong, W.-S. Lee, H.-F. Ng, W.-H. Chiu and W.-T. Wong, *J. Chem. Soc., Dalton Trans.*, 1998, 1043; (*e*) H-L. Wong, Y. Tian and K.-S. Chan, *Tetrahedron Lett.*, 2000, **41**, 7723; (*f*) D. Lötscher, S. Rupprecht, H. Stoeckli-Evans and A. von Zelewsky, *Tetrahedron: Asymmetry*, 2000, **11**, 4341.

